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Hexestrol

A Clinical Study over a Period of 27 Months

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THE DEVELOPMENT of synthetic estrogens has stimulated interest in estrogenic therapy and, since the synthetic estrogens are active orally, it has been possible to extend materially the field of application because of the convenience and inexpensiveness in comparison to the parenteral use of natural estrogens. This has led to a number of clinical reports on the use of estrogens and on the comparative value of synthetic and natural estrogens in the treatment of the menopause, senile vaginitis, hypoestrinism, juvenile vulvovaginitis and for the suppression of lactation.

One fact has definitely been demonstrated: the synthetic estrogens are as effective as the natural and, furthermore, are as efficacious given orally as the natural estrogens given parenterally. It cannot be denied that natural estrogens are ideal, but the convenience of oral administration and the comparative reduction in cost has resulted in a tendency toward a gradual and substantially increased clinical use of the orally active, synthetic estrogens.

In making a clinical appraisal of any estrogen in the treatment of such a condition as the menopause, one must take into consideration a great many factors that may tend to cloud the real biological and physiological action of the medicament used. For example, many menopausal patients feel that they have an illness which gives them an excuse to be "fussed over" continuously by physicians in the hospital, to be "pampered" by their families, or to be supported by welfare organizations without fear of being forced to take a job or be removed from their rolls. Recently another factor has developed which may prolong and aggravate symptoms, namely worry over a son in military service—especially if he is abroad and has not been heard from recently.

For these reasons, we feel that it is impossible to draw reliable conclusions from the clinical study of an estrogen in the treatment of the menopause without correlating clinical results and biological action as evidenced, for example, by a study of the vaginal smear. Obviously there should be some correlation, although not necessarily absolute, between the degree of vaginal epithelial response and the clinical response; otherwise it would be impossible to eliminate psychotherapy as the effective agency.

With these thoughts in mind and with the hope of finding a synthetic estrogen which would give satisfactory clinical result with little or no untoward toxic effects, we planned a long-range clinical experiment in the clinic at Mt. Sinai Hospital. We chose for this study, hexestrol.

DEVELOPMENT AND PHARMACOLOGY OF HEXESTROL

Campbell, Dodds and Lawson (1) in 1938 isolated a substance, di-p-hydroxyphenyl-n-hexane, which was found to produce estrus in all rats to which it was administered in doses of 0.2 microgram.

In a later publication (2) this compound was called hexestrol and its biological activity as assayed in rats was reported. It appeared that, in the laboratory animal, the biological activity was somewhat greater in producing vaginal estrus than that of either diethylstilbestrol or estradiol.

Given orally, hexestrol has from 30 to 50 per cent the activity of diethylstilbestrol; given subcutaneously, the activity is approximately the same as either diethylstilbestrol or alpha-estradiol benzoate (3). Hexestrol produces all the biological actions of a true estrogen. Chronic toxicity studies to date indicate that tissue changes from this compound do not differ from those produced by natural and other synthetic estrogens.

PUBLISHED CLINICAL STUDIES

The first clinical report on the use of hexestrol in human subjects was made by Bishop and coworkers (4). Since the authors were attempting to determine threshold doses rather than clinical results, a clinical correlation of activity was not made. It was noted, however, that unlike diethylstilbestrol hexestrol did not cause nausea.

This report that it produced full estrogenic response without causing nausea spurred on further clinical investigation of hexestrol. In the past few years several such studies have been published, most of them, however, covering administration over short periods of time.

Freed (5) found hexestrol to be effective in controlling menopausal complaints in doses of 3 to 5 mg. daily. With this dosage, the incidence of nausea was about one-half as great as that observed with diethylstilbestrol and it was only occasionally that discontinuance of the drug was necessitated. Barnes (6) used hexestrol successfully in suppressing lactation.

Bieren and Compton (7) found that hexestrol in a series of 80 menopausal patients was satisfactory. In primary dysmenorrhea, in doses of 1 to 20 mg. daily it produced excellent results in 50 per cent of the cycles. Results were satisfactory in treating senile vaginitis. In vulvovaginitis, results with hexestrol were better than with identical amounts of diethylstilbestrol. Withdrawal bleeding occurred in lower incidence than was observed when that drug was used.

McElroy and coworkers (8) found hexestrol actively potent in control of the menopausal symptoms of the surgically castrated woman; untoward side actions were so infrequent as to be considered negligible. Karnaky (9) found hexestrol superior to diethylstilbestrol because of the greatly reduced incidence of nausea and withdrawal uterine bleeding.

Crotty and coworkers (10), reviewing their experience in 358 patients treated with natural and synthetic estrogens over a period of seven years, stated that hexestrol is the most effective of the estrogens used. These authors used both the continuous mass dosage and the "in phase" or intermittent treatment. The average mean treatment time with hexestrol was five and one-half months. Continuous mass dosage of hexestrol resulted in a lesser incidence of complete failures, while the "in phase" administration produced the greater percentage of completely symptom-free results. Hexestrol caused a much smaller percentage of untoward effects than did diethylstilbestrol but had to be

administered in from 3 to 5 times the dosage to secure the same clinical result.

In summary, the published literature covering the clinical use of hexestrol indicates it is a true estrogen, with less disagreeable side actions than diethylstilbestrol. The early reports on the minimal clinical "toxicity" of hexestrol in comparison to diethylstilbestrol prompted us to institute a study of this estrogen in our clinic and this report covers its study over a period of 27 months.

METHOD OF STUDY OF MENOPAUSAL PATIENTS

In this period a total of 105 patients were treated; of these, 80 were menopausal patients (61 natural and 19 surgical). Only the menopausal series was subjected to detailed study and analysis.

Because of the fact that certain symptoms of the menopause are practically indistinguishable from those of neurocirculatory asthenia or psychoneurosis, it was decided to check each patient before and during therapy by means of vaginal smears. We adopted the technic described by Shorr (11), using a differential stain which provides a sharp distinction between the cornified and non-cornified elements. The vaginal smears served both as a diagnostic index and as a guide for the therapeutic use of hexestrol.

All but five menopausal patients were given initially parenteral injections of hexestrol.[1] For comparative purposes, injections of diethylstilbestrol dipropionate were administered to some in an attempt to determine whether that drug in ester form would produce a more prolonged effect. Parenteral injections were used initially because preliminary tests showed that a quicker response was obtained than when oral medication was given, particularly in the severe cases. Hexestrol in oil was used in the first part of the study; both hexestrol in oil and an aqueous suspension of hexestrol were used in the latter part of the study.

Initial dosage was gauged according to the severity of symptoms and follow-up dosage was based on a correlation of clinical response and the percentage increase of cornified cells in the vaginal smears.

When the patient was brought under control with parenteral injections, tablets of hexestrol were given and the dosage was gradually cut down until the level producing symptomatic relief was attained. This maintenance dosage was given for two to four months at which time dosage was gradually reduced further in order to "wean" the patient. We feel that the function of estrogenic medication in the menopause is to bridge the gap and maintain psychomotor and somatic equilibrium between the onset of the initial ovarian insufficiency and the time when natural adjustment to the insufficiency is made.

In such long-range study as this, covering a period of 27 months, opportunity was provided to test individual patients by abruptly withdrawing the oral hexestrol and, for control purposes, administering a placebo ($NaHCO_3$) tablet. This was done for a period of from three to six weeks in a number of patients when symptoms were subsiding or had completely disappeared. During this interval of placebo treatment, symptoms were checked against vaginal smears.

The *dosage* varied with the type of preparation. For hexestrol in oil it was 1 or 2 mg. twice a week or, in severe cases, from 3 to 4 mg. twice a week was given. This dosage was sufficient to control any case, no matter how severe. With hexestrol suspension, only one-half this dosage was required, and was administered only once weekly. (Only rarely was it necessary to give it twice a week.) Upon achieving control of the symptoms with parenteral therapy, 1 to 4 mg. hexestrol was given orally—at first daily. After two to four months of treatment the dose was cut to from 0.5 to 1 mg. daily until it was finally eliminated. One sign that indicated in the occasional undernourished patient that therapy could be discontinued was an increase in the weight.

In table 1 an outline of the treatment schedule of 25 representative cases among the 80 menopausal patients is presented.

This table demonstrates primarily that dosage had to be individualized and that the length of time necessary to bring patients un-

[1] We are indebted to the Wm. S. Merrell Company, Cincinnati, for generously supplying the preparations used and to Dr. R. J. Buckman, Director of Clinical Research of the Merrell Company, for his splendid cooperation in the study.

der control is extremely varied. Some patients received large amounts of hexestrol (45 injections of 1–4 mg. and 522 mg. orally, for example) in comparison to others. Not all the patients are included in this table; our records show that the average mean treatment time of the menopausal patients receiving both parenteral and oral medication was approximately eleven months.

TABLE 1

	Patient	No. Injections (0.5 to 4.0 mg., avg. 1.5 to 2.0 mg. per injection)	Milligrams Orally	Length of Treatment (Mos.)
1	A.M.[1]	48	345	22
2	M.B.	55	78	16
3	B.B.	10	88	14
4	F.B.	20	21	12
5	G.C.	10	305	16
6	B.D.	20	105	5
7	E.F.[2]	20	275	27
8	M.F.	20	210	18
9	F.G.	30	80	7
10	M.H.	20	277	19
11	D.H.	30	575	27
12	S.J.	20	65	7
13	B.K.	10	150	10
14	B.K.	20	42	7
15	B.M.	30	80	12
16	E.M.	45	522	27
17	C.P.	20	25	16
18	R.S.	20	146	16
19	F.S.	20	142	16
20	B.S.	20	333	20
21	L.S.	10	155	24
22	J.S.	10	333	22
23	B.S.	10	110	17
24	A.W.	20	271	24
25	D.A.	20	110	14

[1] Bleeding occurred after the 40th injection hence treatment was omitted for two months.

[2] Slight gastro-intestinal disturbance was experienced at the beginning of the oral treatment.

RESULTS

Results were appraised by a correlation of clinical response and the percentage increase of cornified vaginal epithelial cells. A preliminary test indicated that improvement was not brought about as quickly when tablets were used at the beginning of treatment as when injections were given.

The results of the study may be recapitulated.

Hexestrol proved to be a true estrogen in that it controlled the clinical symptoms of estrogen deficiency and produced the characteristic estrus type of vaginal smear.

Almost all of the patients showed definite improvement after the seventh injection and practically all were symptom-free after the first 10 to 20 injections. In aqueous suspension the drug was more effective and had a longer lasting action than did hexestrol in oil or diethylstilbestrol dipropionate.

In tablet form it provided a very effective means of maintaining estrogen balance after the symptoms were brought under control by parenteral injections. The tablets were well tolerated. Since they were available in various dosage forms, the quantity could be reduced conveniently as conditions warranted.

When in a test group the symptoms were being effectively controlled with hexestrol tablets and placebo tablets were substituted there was a return of symptoms in all instances, showing that the effect of the hexestrol was not psychic.

Vasomotor symptoms such as flushing, dizziness, etc., were effectively stopped. Blood pressure was lowered when its elevation was a part of the menopausal syndrome. Excessive falling of hair was arrested in the severe menopausal cases. Relief of various rheumatic and arthritic complaints and symptoms often accompanying the menopause was obtained. Marked increase of weight occurred in those patients who were debilitated and undernourished, when proper dosage and control of symptoms were established.

Untoward effects were very slight; two patients experienced slight nausea and one patient, headache. The gastro-intestinal disturbances were easily controlled by reducing the dosage. It was not necessary to discontinue administration of the drug. Excessive bleeding during the menses or after a long amenstrual period could readily be eliminated in most cases by reduction of dosage and in the remaining few by stopping treatment for a short period.

Attention is called to the long duration of the study and the large total amounts of hexestrol given to several of the patients with complete freedom from untoward effects. For example, one patient received 45 parenteral injections of 1–4 mg. of hexestrol and 522 mg. orally over a period of 27 months; another, 30 injections and 575 mg. orally for the same period.

SUMMARY AND CONCLUSIONS

Hexestrol was used over a period of 27 months and was given parenterally and orally to a total of 105 estrogen-deficient patients, 80 of whom were menopausal. It was effective in all cases. A detailed account of only the menopausal series is included in this report.

Hexestrol is a true estrogen, as evidenced by clinical response and examination of vaginal smears.

In the 80 menopausal patients (61 natural and 19 surgical) hexestrol brought about control of symptoms in all cases, with freedom from side actions in all but two who had slight nausea, which was overcome by reduction of dosage. Clinical response was correlated with biological response by differential staining of vaginal smears.

The initial use of parenteral injections of hexestrol until the symptoms were brought under control, followed by minimal maintenance levels of the drug given orally proved to be the procedure of choice, since it produced clinical improvement more rapidly than when only oral administration was employed.

Aqueous suspension of hexestrol was superior per unit of weight to hexestrol in oil in being more active and in producing more prolonged effect, necessitating injection only once a week, even in severe cases.

The average mean treatment-time in the menopausal series was approximately 11 months. The large total dose given in several cases and the absence of untoward effects demonstrates the relative non-toxicity of hexestrol and its clinical safety when administered under controlled medical supervision.

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Excretion of Neutral 17-Ketosteroids in Adrenal Cortical Tumor and Feminine Pseudohermaphroditism with Adrenal Cortical Hyperplasia

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ONE OF THE striking characteristics of functioning tumors of the adrenal cortex is the variety and variability of the clinical pictures which they produce. Even a cursory review of the reported cases and a glance at the photographs which usually accompany the case reports are sufficient to satisfy anyone who is skeptical regarding the truth of this statement. Such a review shows not only that the often described classical clinical pictures are different among boys, girls, men and women, but that grossly similar tumors produce widely different clinical effects even among members of the same sex and age groups. In some instances only one or two striking endocrine abnormalities will be present, to the relative or absolute exclusion of others. Some patients will be extremely weak; others unnaturally vigorous. Some will have striae, or hypertension, or diabetes or polycythemia, or all of these; others will not. Some cases present in all details the syndrome described by Cushing; in others the appearance of the patient will be totally different. In brief, the differences in clinical manifestations are not merely differences in degree but are differences in kind as well.

All this is not surprising. Clinical and experimental evidence indicates that the adrenal cortices probably have more than one and may have several functions, which in turn may or may not be related. The fact that more than 25 adrenal cortical compounds have been isolated is only one of the several foundations supporting the preceding generalization. Furthermore, the hormonal properties of some of these compounds are remarkably different, both qualitatively and quantitatively. With abnormal adrenal cortices, such as occur in cases of functioning adrenal cortical tumor, additional variables are introduced. These tumors function independently of the needs of their host. Their hormonal influences do not seem to be subject to normal controlling influences. The tumors differ one from another in their histologic appearance and in their degree of malignancy. Regarded clinically they have all the earmarks of an actively hyperfunctioning lesion. From these considerations, one would suspect them to be capable of secreting excessive amounts of any one or even all of the compounds that have been extracted from the adrenal cortex. In addition, one would expect, particularly from the variations encountered in the clinical pictures, that these tumors differ one from another in their qualitative and quantitative hormonal potentialities. If this were the case, the urinary excretion of hormonal products, including the

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17-ketosteroids,[2] would vary materially from case to case.

To a certain extent, the same reasoning is applicable to the hyperplastic adrenal cortex.[3] Here, however, the foundations of the argument are less secure than in the case of adrenal cortical tumors. Bilateral adrenal cortical hyperplasia is not a clinical entity and barely can be called a pathologic entity. Glands of this type are observed accidentally at necropsy in cases of basophilic tumors of the anterior pituitary body, in some cases of thymic tumors, in feminine pseudohermaphroditism, in cases of Cushing's syndrome without basophilic tumors of the pituitary body and in acromegaly. In these different conditions there is the possibility that different basic cellular elements of the cortex predominate in the hyperplastic process to the relative or even absolute exclusion of others (1, 2). For example, in pseudohermaphroditism one might suspect that only the so-called androgenic cortical cells are involved. On purely clinical grounds one certainly would hesitate to attribute identical pathophysiologic activities to the hyperplastic adrenal cortices of pseudohermaphroditism, pituitary basophilism and acromegaly.

So much for the theory—what are the facts? Qualitative, and to a certain extent quantitative, variations of urinary excretion of hormonal and other substances have been demonstrated in cases of functioning adrenal tumors (3–9). In cases of hyperplastic adrenal cortices with endocrine symptoms, there is insufficient evidence to permit generalization. The purpose of the present report is to call attention to the quantitative variability of the total urinary excretion of neutral 17-ketosteroids as it occurred in our cases of functioning adrenal cortical tumors and feminine pseudohermaphroditism with cortical hyperplasia. In most instances the α and β fractions were not determined separately.

[2] The terms *17-ketosteroids* and *androgens* are often confused. Not all of the 17-ketosteroids are androgens, nor are all of the androgens 17-ketosteroids. Among normal men, the 17-ketosteroids have a dual source, namely the testicles and the adrenal cortices. Among women most, if not all, of these steroids which are found in the urine are derived from the adrenal cortices.

[3] At present there are no universally accepted histologic criteria by which adrenal cortical hyperplasia can be recognized. Consequently, such statements as "hyperplastic adrenals were found at operation" or "at necropsy" convey little precise information. They usually imply that the adrenal glands were larger than normal and that the enlargement appeared to be cortical rather than medullary.

CLINICAL MATERIAL

Eleven patients were studied. Eight had functioning adrenal tumors that were removed surgically. All eight survived the operation. All eight had in varying degrees the well-known and frequently described endocrine symptoms that accompany these tumors.[4] Six patients were relieved entirely of these symptoms by removal of the tumor; one patient died ultimately of metastasis; another, on whom operation was performed recently, improved but has not had sufficient time to return to normal.

Three patients were feminine pseudohermaphrodites. The diagnosis was established at laparotomy by examination of the internal genital organs. In one case a hyperplastic adrenal was removed surgically, in the other two the adrenals were palpated through the laparotomy incision and were thought to be enlarged. In the latter two cases, although the possibility of adrenal tumor was excluded almost completely, the exact anatomic status of the adrenals is open to question. However, the high incidence of cortical hyperplasia among pseudohermaphrodites makes the diagnosis probable.

METHODS AND RESULTS

Before surgical exploration was performed, accurately-timed, 24-hour specimens of urine were collected in bottles which contained 5 to 10 cc. of concentrated hydrochloric acid. The fresh specimens were boiled for ten minutes after addition of 0.1 volume of concentrated hydrochloric acid and then were extracted thoroughly either with benzene or with carbon tetrachloride. These extracts were partially purified, essentially according to the procedure of Talbot and co-workers (10). In the earlier determinations (*Cases 1, 2, 6, 7,* and *10*) benzene was used and the colorimetric assay for 17-ketosteroids was performed according to the method of Holtorff and Koch (11). The other specimens were extracted with carbon

[4] The clinical features of these cases will be the subject of a separate report.

tetrachloride and the absolute alcohol technic of Callow and associates (12, 13) was used together with a correction equation to compensate for the overestimation due to nonketonic chromogens [Fraser and co-workers (14); Talbot and co-workers (15); Engstrom and Mason (16)]. Table 1 summarizes the data thus obtained.

The wide variations in excretion of total 17-ketosteroids exhibited by these cases are seen clearly from these data. Two infants having tumors excreted comparatively slight amounts of 17-ketosteroids. These values may be abnormally high for such young individuals even though the increases were slight (17). The diagnostic significance of this variability in the total excretion of 17-ketosteroids is self-evident and needs no comment. Also, it is clear that patients having adrenal tumors do not always excrete more total 17-ketosteroids than patients having cortical hyperplasia. The determination of α and β fractions of the neutral 17-ketosteroids has been utilized by Talbot and co-workers (18) to distinguish those patients who have adrenal tumor from those suffering from adrenal hyperplasia. We have not accumulated sufficient data to evaluate the usefulness of this criterion.

TABLE 1. EXCRETION OF 17-KETOSTEROIDS

Case	Age, years	Sex	Specimens collected	Average 17-ketosteroid excretion per 24 hours, mg.
Adrenal cortical tumor				
1	1½	M	2	2.8[1]
2	1¼	F	1	3.0[1]
3	63	F	2	45.6
4	16	F	1	54.6
5	25	F	3	131.0
6	3½	F	1	170.0
7	21	F	3	240.0
8	45	F	4	857.0
Adrenal cortical hyperplasia with feminine pseudohermaphroditism				
9	3		2	13.5
10	5		1	37.0
11	19		2	75.2

[1] Because of the age of these patients and the difficulties involved in collecting accurate twenty-four hour specimens these values may be too low. It is very unlikely that this error is greater than −50 per cent.

SUMMARY

The excretion of neutral 17-ketosteroids in the urine of eleven patients ranged from 2.8 mg. to 857 mg. per 24 hours. Eight of the patients had functioning adrenal cortical tumors and three were feminine pseudohermaphrodites who had adrenal cortical hyperplasia. Two infants having tumors excreted comparatively slight amounts of 17-ketosteroids, and one of the patients with pseudohermaphroditism excreted normal amounts. All of the others excreted abnormally large amounts. Patients having functioning adrenal tumors do not always excrete more total 17-ketosteroids than patients having cortical hyperplasia.

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Sublingual Absorption of Progesterone and Anhydrohydroxyprogesterone

I. Endometrial Studies[1]

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INTRODUCTION

IT IS AN accepted fact that ingested progesterone is destroyed. On the other hand, ingested anhydrohydroxyprogesterone (17-ethinyl testosterone) is effective. It has been shown that the perlingual absorption of estradiol is superior to the stomachal or oral absorption (1). The administration of steroids by the sublingual route has in certain instances advantages of convenience. Sublingual administration of methyl testosterone has yielded at least as favorable results as has the oral administration (2).

This paper deals with the absorption sublingually of a) pure crystalline progesterone and b) anhydrohydroxyprogesterone (1). The only previous work on the subject is that of Joel (3), in which anhydrohydroxyprogesterone was administered sublingually. Evidence of effective absorption of this preparation was seen in the subsequent secretory change in the endometrium which had been primed in advance by estradiol given sublingually. The criticism that proof of sublingual absorption of anhydrohydroxyprogesterone is not convincing, inasmuch as the drug may be swallowed, does not hold for progesterone. Since progesterone is destroyed by the gastric juices, its effectiveness must depend wholly on its absorption by way of the oral mucosa.

METHODS

In the study herein reported specially compressed 2.5 and 5 mg. linguets of pure crystalline progesterone and 5 mg. linguets of anhydrohydroxyprogesterone specially prepared for sublingual application were employed. The usual dosages were 15 to 50 mg. per day over a period of three to seven days, although smaller dosages over larger periods of time were given for various conditions. The criteria for effective absorption were: a) the induction of "progesterone-withdrawal bleeding" in amenorrheic patients and b) the effective arrest of menorrhagia six to ten days after the withdrawal of the drug. The expression "bleeding arrested according to plan" is used in this paper to describe this phenomenon. Endometrial biopsies were taken when feasible prior to and after administration of a course of progestins. This paper deals with the interpretation of endometrial biopsies in relationship to effectual absorption.

ENDOMETRIAL STUDIES

Of six patients receiving progesterone linguets and in whom endometrial studies were performed one or two days after cessation of therapy or soon after the occurrence of bleeding, endometrial biopsies were performed before onset of therapy in three. In nine patients,

[1] A grant-in-aid of research for this study was made by the Ciba Pharmaceutical Products Inc. to the University of Georgia School of Medicine.

[2] This work was completed before the author's entrance into the Service. Present address: Robert B. Greenblatt, Surgeon (R) U. S. Public Health Service—Southeastern Medical Center, Oatland Island, Savannah, Georgia.

TABLE 1. PROGESTERONE LINGUETS

No.	Name	Diagnosis	Date[1]	Dosage and Dates	Date[1]	Results
1	J.C.	Amenorrhea-Menorrhagia Syndrome[2]	7/15-E$^+$	150 mg. 7/15–19/	7/20-E$^+$	Withdrawal bleeding
2	T.T.	Functional Amenorrhea	2/2-E	125 mg. 2/11–13/	2/17-E	Withdrawal bleeding
3	W.R.	Functional Amenorrhea	—	150 mg. 7/9–14/	7/22-E	Withdrawal bleeding
4	L.W.	Primary Amenorrhea	—	62.5 mg.[3] 7/5–9/	7/10-E	Withdrawal bleeding
5	L.S.	Menorrhagia[2]	—	200 mg. 7/8–12/	7/14-E	Withdrawal bleeding
6	T.N.	a) Functional Amenorrhea	7/9-E	150 mg. 7/9–13/	7/14-E	Withdrawal bleeding
		b) —	—	250 mg.[4] 7/20–29/	7/29-P$^-$	Bleeding started before cessation of therapy
		c) —	—	182.5 mg. 8/4/14/	8/15-E	Bleeding started before cessation of therapy

[1] Date of suction curettage.
[2] Treatment during amenorrheic phase.
[3] Primed with 4 mg.—estradiol—orally.
[4] Primed with 1 mg.—estradiol dipropionate parenterally.
E$^+$ Cystic glandular hyperplasia.
E Estrogenic endometrium.
P$^-$ Imperfect progestinal endometrium.

TABLE 2. ANHYDROHYDROXYPROGESTERONE LINGUETS

No.	Diagnosis	Date[1]	Dosage and Dates	Date[1]	Results
1. G.M.	a) Menorrhagia[2]	4/25/-E	105 mg. 4/25–27/	4/30-M	Withdrawal bleeding
	b) —	6/2/-E$^+$	165 mg. 6/3–7/	6/9-P	Withdrawal bleeding
2. E.K.	Menorrhagia[2]	6/1/-E	120 mg. 6/1–5/	6/8-E	Withdrawal bleeding
3. C.S.	Menorrhagia[2]	5/15-E	180 mg. 5/15–26/	5/22-Ps 5/29-P	Withdrawal bleeding
4. L.W.	Primary Amenorrhea	6/2/-E$^-$	100 mg.[3] 6/2–6/	6/9-E	Withdrawal bleeding
5. R.H.	Functional Amenorrhea	—	125 mg. 5/12–16/	5/19-E	Withdrawal bleeding
6. C.R.	a) Functional Amenorrhea	—	125 mg.[4] 1/15–17/	—	No withdrawal bleeding
	b) —	—	105 mg. 1/26–28/	2/2-E	No withdrawal bleeding
7. N.N.	Menorrhagia	5/15/-E$^+$	100 mg. 5/15–18/	5/20-E$^+$	Bleeding arrested according to plan
8. L.S.	Menorrhagia	6/16/-E$^+$	200 mg. 6/16–19/	6/20-M	Bleeding arrested according to plan
9. W.R.	Menorrhagia	6/5/-E$^+$	140 mg. 6/5–8/	6/10-E$^+$	Failure to arrest bleeding

[1] Date of suction curettage.
[2] Treated during amenorrheic phase.
[3] Primed with 7.5 mg. estradiol orally.
[4] Primed with 5 mg. stilbestrol parenterally.

E Estrogenic endometrium.
E$^+$ Cystic glandular hyperplasia
E$^-$ Atrophic endometrium
P Progestinal endometrium.
Ps Presecretory endometrium.
M Mixed estrogenic and progestinal phase or imperfect endometrium.

endometrial biopsies were obtained after courses of anhydrohydroxyprogesterone sublingually and in seven of these endometrial studies were also performed immediately before onset of therapy. Two sets of biopsies were performed in one patient; in another a biopsy was performed before, during and after therapy. Tables 1 and 2 list the dosages employed, the endometrial findings and the results of therapy.

INTERPRETATION

In the series of cases in which progesterone linguets were employed the endometrium remained persistently estrogenic with but one exception in the eight instances. An imperfect progestinal endometrium resulted in this particular instance following the largest dosage used in this series, to wit, 250 mg. of progesterone sublingually. Significant, too, may be the fact that the patient (*Case 6b*, table 1) was adequately primed with an estrogen.

Since withdrawal bleeding occurred in six of the eight instances in this series, it must be assumed that effectual absorption occurred. In two the results were questionable, since uterine bleeding occurred before therapy was completed and was not followed by withdrawal bleeding. An analysis of the ten endometrial biopsies obtained after administration of anhydrohydroxyprogesterone sublingually revealed that in six instances the endometrium persisted in the estrogenic phase; in two, there was a mixed or imperfect endometrium and in two there were progestinal changes. Of the two showing a complete secretory phase there is room for doubt in one (*Case 3*, table 2), because in the interim between the first and last biopsy the patient may have ovulated spontaneously. In *Case G. M.* (1-b, table 2) the secretory changes may well be attributed to the medication, since only seven days elapsed between the findings of an hyperplastic estrogenic endometrium and a progestinal one. Joel (3) obtained secretory changes in the endometriums of the six women treated with 150 mg. doses of anhydrohydroxyprogesterone sublingually after priming with 60–90 mg. of estradiol sublingually. His proof for the effective absorption and utilization of anhydrohydroxyprogesterone rested in the secretory changes that followed. In the present series, priming with estrogens was done only in occasional instances and then with comparatively small doses. This fact may account for the failure to obtain true secretory changes more frequently. Then, again, the dosage of anhydrohydroxyprogesterone used in this series was for the most part below 150 mg. In those instances in which more than 150 mg. was used, it appears that partial or complete secretory changes were obtained. Since withdrawal bleeding occurred in six of the nine instances following cessation of therapy and "arrest of bleeding according to plan" occurred in two of three instances, it may be assumed that the amount needed to produce this effect is much less than that needed to produce secretory changes.

SUMMARY

Endometrial studies were performed following sublingual application of specially prepared linguets of progesterone and anhydrohydroxyprogesterone. The dosage for the former in this series was 62.5–250 mg. and for the latter 105–200 mg. The medication was usually administered over a period of three to ten days. In general, the endometrium with but few exceptions persisted in the estrogenic phase. Mixed, imperfect progestinal or progestinal changes were obtained in several instances with the larger dosages. The frequency with which withdrawal bleeding or "the arrest of bleeding according to plan" was obtained suggests effective absorption sublingually of both progesterone and anhydrohydroxyprogesterone and that the dose needed to produce this reaction is much below the level needed to change an estrogenic endometrium to a progestinal one. The criticism that proof of sublingual absorption of estradiol, methyl testosterone or anhydrohydroxyprogesterone is not convincing inasmuch as part of these drugs may be swallowed does not hold for progesterone. It is possible, therefore, since progesterone is inactivated after ingestion but is active after sublingual absorption, that the other steroids may also behave in the same way.

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Utero-Thermometry

A Study of Uterine Temperature during Reproductive Life, Menopause, and Amenorrhea

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MEASUREMENTS of the basal body temperature of the female have been made ever since the invention of the thermometer but recently the matter has assumed new importance in connection with the problem of ovulation and sterility (Rubenstein (1), Rubenstein and Lindsley (2), Zuck (3), Palmer and Devillers (4), Palmer (5), and Martin (6)).

Hitherto rectal measurements have been utilized but it seemed desirable to investigate whether the uterus, with its immediate response to ovarian hormones, might not afford a better index. The uterine temperature of both the corpus and the cervix has therefore been recorded in 32 women exhibiting a normal menstrual cycle. A series of 24 women in the menopause and of 36 patients with secondary amenorrhea were also studied. To permit comparisons with the uterine temperatures, those of the vagina, rectum, mouth, and axilla were recorded in addition.

A special thermometer[1] was devised for taking the temperatures of the uterine cavity and the cervical canal (fig. 1). In principle, it is a mercury-containing, angulated thermometer made of strong glass. It consists of a shorter arm of 8 cm. carrying the mercury column and a longer arm of 8½ cm. containing the scale. The length of the mercury container is 2½ cm. The arms form an angle of 161 degrees corresponding with the corporal-cervical angulation. The usual angle of the uterine probe measures 168 degrees. During the initial temperature determinations, it became apparent that the smaller angle is more suitable. Due to its adequate angulation introduction of the instrument into the corpus uteri is easily accomplished by using the thermometer like a uterine sound. However, with less experience it is better to probe the uterus before introducing the thermometer. In some cases the procedure is facilitated by steadying the uterus. This can be accomplished by grasping the anterior cervical lip with a tenaculum. There is no danger of breakage either in introducing the thermometer or when it is *in situ* if forceful manipulations are avoided. The mercury has to be placed completely within the corpus of the uterus, when taking the uterine, and completely in the cervical canal, when taking the cervical temperature. Omission of this cardinal rule will yield erroneous results. In taking the uterine temperature all the principles of asepsis and antisepsis have to be followed painstakingly. The thermometer must be sterilized and only sterile instruments and gloves used. Sterilization is best achieved by keeping the thermometer in a glass receptacle containing a 1:1,000 solution of bichloride of mercury. The instrument is thoroughly dried with a sterile sponge before introduction into the uterine cavity.

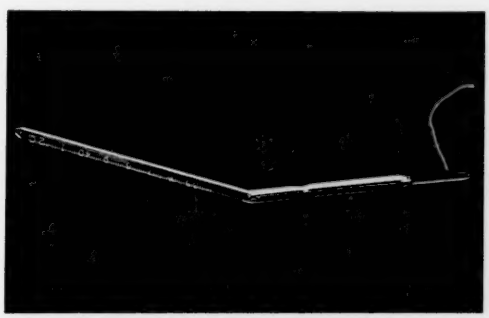

FIG. 1. Thermometer for taking temperatures of uterine cavity and cervical canal.

Breakfast should be omitted prior to taking the temperatures which should always be recorded at the same hour in the morning.

Figure 2 is a record of the average corporal (uterine), cervical and vaginal temperatures of the 32 normally menstruating women studied, 14 of whom exhibited a 28-day rhythm, 12 a

[1] The thermometer may be obtained from the Ex-Ell Instrument Corp., Brooklyn, N. Y.

cycle of from 25–27 days and 6 a 27–29 day cycle. These observations comprise a total of 150 menstrual cycles. Analyzing the corporal curve, it appears that the lowest temperature (37.3° C.) occurs postmenstrually—the fifth day of the cycle—and that the temperature served a decline of temperature to the minimum postmenstrually (37.3° C.).

The pattern of the vaginal temperature curve follows closely the corporal curve, the level of the vaginal temperature being consistently lower. The cervical curve, except for a

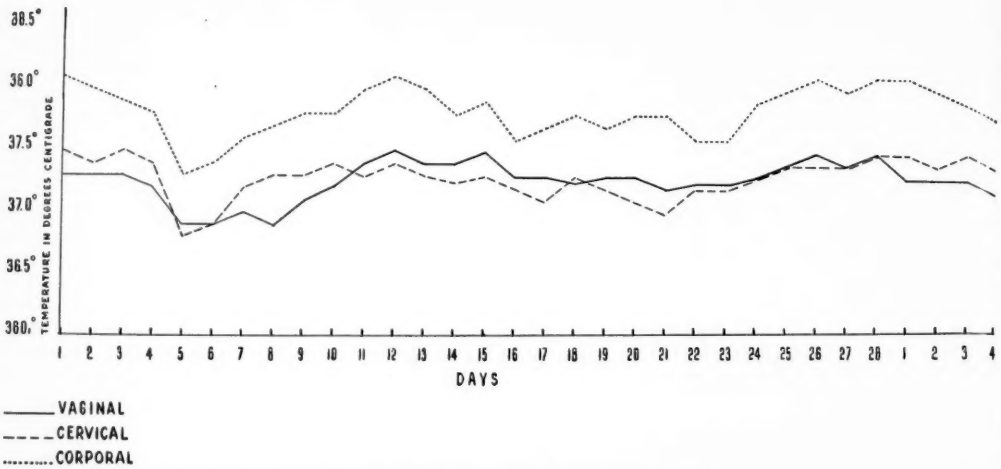

FIG. 2. Average curves constructed from corporal, cervical and vaginal temperature measurements recorded in 32 normally menstruating women.

then climbs gradually to reach a peak (38.1° C.) on the 12th day—around the time of ovulation. Thereafter, there are fluctuations of the curve with another high (38.1° C.) becoming manifest between the 26th and 28th day of the cycle, i.e., premenstrually. During the flow we observe a decline of temperature to the minimum postmenstrually (37.3° C.).

The pattern of the vaginal temperature curve follows closely the corporal curve, the level of the vaginal temperature being consistently lower. The cervical curve, except for a low temperature postmenstrually (36.8° C.) and a peak premenstrually (37.5° C.), does not exhibit such marked wave-like fluctuations as those of the corporal and vaginal curves.

Figure 3 shows the average rectal, oral and axillary temperatures of the same women,

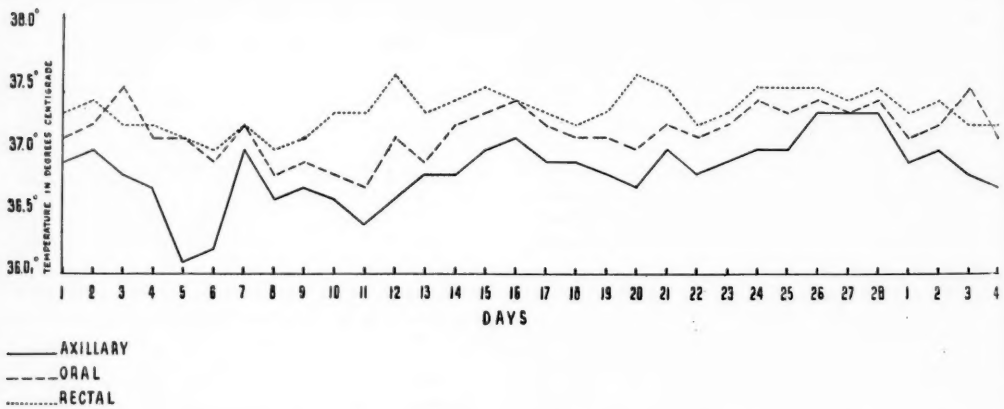

FIG. 3. Average curves constructed from rectal, oral and axillary temperature measurements recorded in same subjects as in figure 2.

whose measurements are shown in figure 2. The course of the rectal curve exhibits certain similarities with the corporal and vaginal graphs. Again the lowest readings are encountered during the postmenstrual phase with a rise of temperature on the twelfth day of the cycle. This peak of the rectal temperature coincides with the mid-interval peak characteristic of the corporal and vaginal temperature. The remainder of the rectal curve is not noteworthy except that the temperature level from the twelfth day on is higher than that up to this time. Also, the curves portraying the oral and axillary measurements show a tendency toward higher temperatures during the second half of the cycle. It would appear then that the corporal measurements most distinctly reflect the cyclic ovarian changes which occur during reproductive life.

The absence of marked temperature fluctuations in climacteric women proves that the changes are conditioned by the cyclic activity of the gonads. In the series of 24 women in the menopause it was found that there were two groups, one with generally lower, another with higher temperature levels. The former were predominantly women in the early stages of their menopause with corporal temperatures averaging 37.4° C. The latter were women who had gone through the change of life many years before and their mean corporal temperature was almost 38° C.

Table 1 shows the mean temperatures of the corporal (uterine), vaginal, rectal and oral measurements of three representative cases of both groups. Temperatures were taken daily over a period of from four to six weeks and the respective averages calculated. In the column pertaining to corporal temperature also the maximal and minimal values are registered.

Notwithstanding slight oscillations of the individual measurements, no rhythmic, wave-like fluctuations of the temperature typical of normally menstruating women were observed in either of these groups.

In order to evaluate the influence of hormone administration on the corporal temperature of women in the menopause, estradiol benzoate[2] and progesterone[2] were given cyclically in six climacteric patients. The following case history exemplifies both procedure and observations.

Patient St. L., aged 56, para-1, complained of bloody vaginal discharge, flushes and frequency of micturition. The menstrual history was normal in every respect. Menses ceased seven years ago. Gynecological investigation revealed a senile vaginitis characterized by small hemorrhagic areas scattered over the vaginal walls and the cervix. The anteverted and anteflexed uterus was small and atrophic. There were no indications of any disease of either the adnexa or the parametria. No bacteria were found in the smear and trichomonas vaginalis was also absent. A specimen of the vaginal secretion contained numerous leukocytes and had a pH of 6.0. Medical examination revealed no abnormalities.

TABLE 1. MEAN TEMPERATURE IN THE MENOPAUSE

Initials	Age	Duration of Menopause	Corporal			Vaginal	Rectal	Oral
			Min.	Max.	Average	Average	Average	Average
E.M.	48 yr.	1 yr.	37.3	37.6	37.4	36.9	37.0	36.7
G.M.	46 yr.	1½ yr.	37.4	37.6	37.5	37.1	37.2	36.5
M.K.	51 yr.	3 yr.	37.2	37.4	37.3	36.6	36.7	36.5
A.R.	67 yr.	16 yr.	37.5	37.8	37.7	37.4	37.3	36.8
R.J.	65 yr.	17 yr.	37.8	38.1	38.0	37.6	37.5	36.8
J.St.	65 yr.	17 yr.	37.7	38.0	38.0	37.6	37.7	36.6

During a 10-day period of observation regular corporal measurements were taken; the minimal temperature recorded was 37.5° C., the maximal 37.9° C. The mean of 37.6° C. was calculated from ten readings on consecutive days. Following this control period, four doses of estradiol benzoate—10,000 R.U. each—were administered over a period of two weeks. By then the vaginitis had cleared up and the flushes had subsided. Following a 3-day interval without medication 10 mg. progesterone was given every other day for five doses. The minimal corporal temperature during estrogen administration was 37.3° C., the maximal 37.6° C. During progesterone medication the temperatures were higher, ranging from 37.7° C. to 38.0° C.

Two days following discontinuation of progester-

[2] The estradiol benzoate (Dimenformon Benzoate) and the progesterone (Progestin 'Roche-Organon') administered to the menopausal and amenorrheic patients presented were supplied through the courtesy of Dr. L. Pirk of Roche-Organon, Inc., Nutley, New Jersey.

one, bleeding ensued, lasting 2½ days. The corporal temperature taken after cessation of bleeding was 37.3° C.

These readings indicate that cyclic hormone administration to a great extent normalizes the corporal temperature curve of a climacteric woman. There is a peak prior to bleeding with a definite drop of the temperature following termination of the flow. However, there is no mid-interval peak.

Measurements taken in the series of 36 patients with amenorrhea revealed the absence of marked fluctuations corresponding to the analogous status of women in the menopause. The impression was gained that cases of long-lasting amenorrhea exhibit higher temperature levels than those of shorter standing. It almost seems that there exists a parallelism between the corporal temperature and the duration of the disorder. One cannot help but presume that the two groups of menopausal women—those with lower temperatures in the early and those with higher values in the later stages—have their respective counterparts among patients with amenorrhea. Hormone administration influenced the temperature curves in a way similar to its effect in the climacteric woman.

Originally, the treatment plan used was that of Kaufmann. Pre-medication temperatures were recorded for a month and the measurements were continued during hormone treatment. An illustrative case history follows.

Patient E. A., aged 35, para-2, complained of amenorrhea of 12 months' duration. Menarche occurred at 12½ years; menstruation was regular at four-week intervals with the bleeding lasting 3–4 days. Following her first delivery 13 years ago, the menses became scant and there was concomitant headache. Simultaneously, with the onset of the amenorrhea the patient became nervous, irritable, and had spells of Quincke's edema. Gynecological investigation revealed normal external genitalia. A yellowish discharge was present which consisted of leucocytes, squamous-cell epithelia, a mixed flora of gram-positive and gram-negative bacteria and cocci. The pH of the vaginal discharge was 5.5. The anteverted and anteflected uterus was small and atrophic. The adnexa and parametria appeared to be normal. Following a month of observation, hormonal treatment was instituted. First, 5 intramuscular injections of estradiol benzoate—10,000 R.U. each—were administered semi-weekly. After a three-day interval, 10 mg. progesterone was given twice a week for 5 doses. Bleeding starting 48 hours after the last injection and lasting three days resulted.

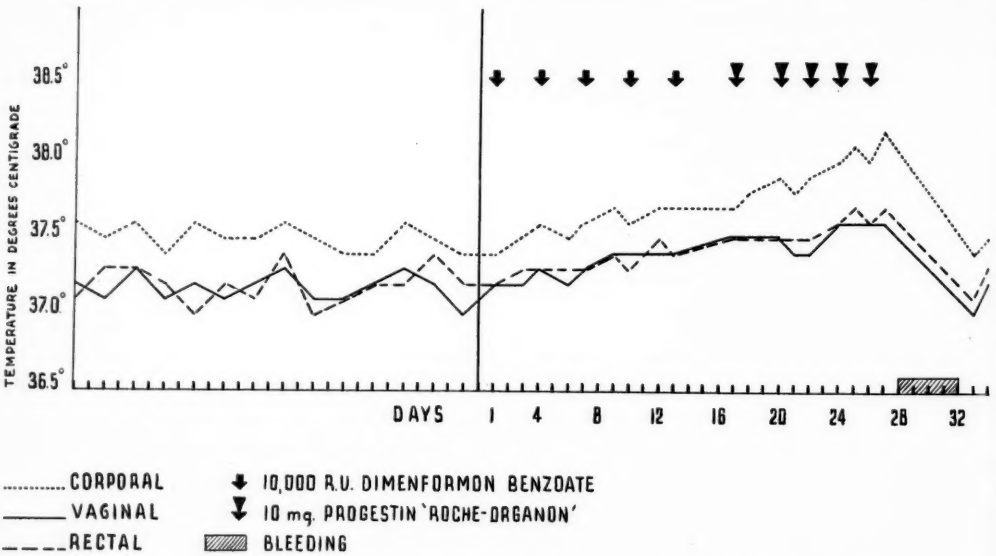

FIG. 4. Curves of corporal, vaginal and rectal temperatures recorded in amenorrhea of 12 months' duration prior to (left side of dividing line) and during hormone medication (right side of dividing line).

Figure 4 portrays the corporal, vaginal and rectal temperatures taken prior to and during

medication. Particularly the corporal pre-medication measurements show only slight fluctuations. Estrogenic medication caused a gradual rise in the temperature with a more marked ascent when luteal hormone was administered. The peak prior to the bleeding and the marked drop of temperature afterward, observed both in normal women of reproductive age and in climacteric patients who had been subjected to cyclical hormone treatment, were also observed in this patient with amenorrhea toward the end of progesterone administration. The graph shows that there was no mid-interval peak, as was true also in climacteric patients after hormone administration and which is so characteristic of a normally menstruating woman.

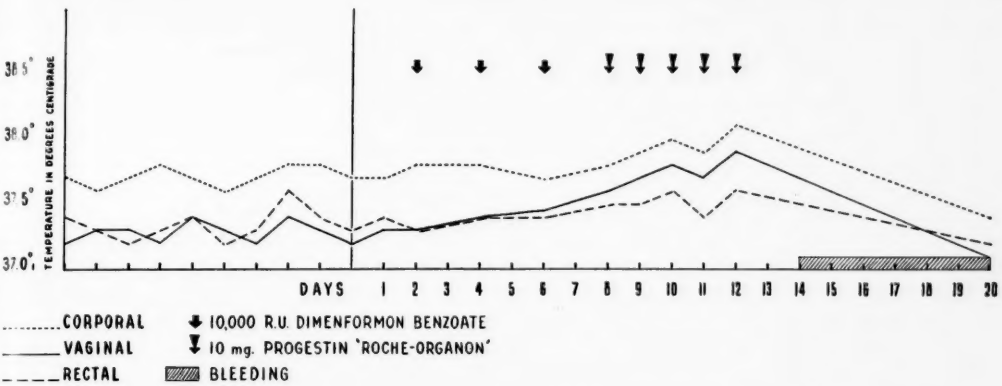

FIG. 5. Curves of corporal, vaginal and rectal temperatures recorded in amenorrhea of 7 months' duration prior to (left side of dividing line) and during hormone medication (right side of dividing line).

Since the pre-medication measurements in women with amenorrhea in our series up to 1941 followed the same pattern, later it was decided to carry out the control measurements over a reduced time interval only. The graphs obtained in an average of ten days reflect perfectly the character of the temperature curve of a much longer period of time. Moreover, in view of the tendency in recent years to shorten the duration of treatment, therapy in 22 patients was modified by giving 3 or 4 injections of estradiol benzoate, 10,000 R.U. each, every other day. After a two-day interval, progesterone in dosages of 10 mg. was given on each of 4 or 5 consecutive days. Except for one patient whose uterus exhibited a high degree of atrophy, in all cases bleeding lasting from 3 to 5 days followed this treatment plan. Figures 5, 6, and 7 portray the corporal, vaginal, and rectal temperatures taken prior to and during treatment of three typical cases (duration of the amenorrhea 7 months, 8 months, and 3 years respectively). The age of these patients ranged from 21 to 29 years; their menstrual history had been normal prior to cessation of bleeding, except for the patient with the amenorrhea of longest standing (fig. 7). This woman had been irregular with intervals of sometimes 2–3 months for 3 years before the onset of the amenorrhea. Gynecological examination revealed normal external genitalia in all three patients; the uteri were small in all instances and the vaginal mucosa atrophic to some extent. The corporal pre-medication measurements, plotted to the left side of the vertical dividing line on the graphs, again show only slight fluctuations. The curves to the right of the dividing lines portray the temperatures during hormone administration. Estrogenic medication does not evoke any significant rise in the corporal temperature but higher values were observed under progestogenic treatment. Again there was a drop of the temperature after the bleeding.

The comparatively high pre-medication temperature exhibited by the amenorrhea case of 3 years' standing (fig. 7) showed a trend toward normalization, following estrogen administration.

The temperature peak occurring premenstrually in normal women of reproductive age and also in climacteric women and patients with amenorrhea following progesterone administration leaves little doubt that the corpus luteum hormone is responsible for this phenomenon. The mid-interval peak observed in healthy women was not reproduced by cyclic hormone administration in either climacteric women or patients with amenorrhea.

DISCUSSION

The basal body temperature of normally menstruating women exhibits wave-like fluctuations. These changes are reflected wherever the body temperature may be taken and are

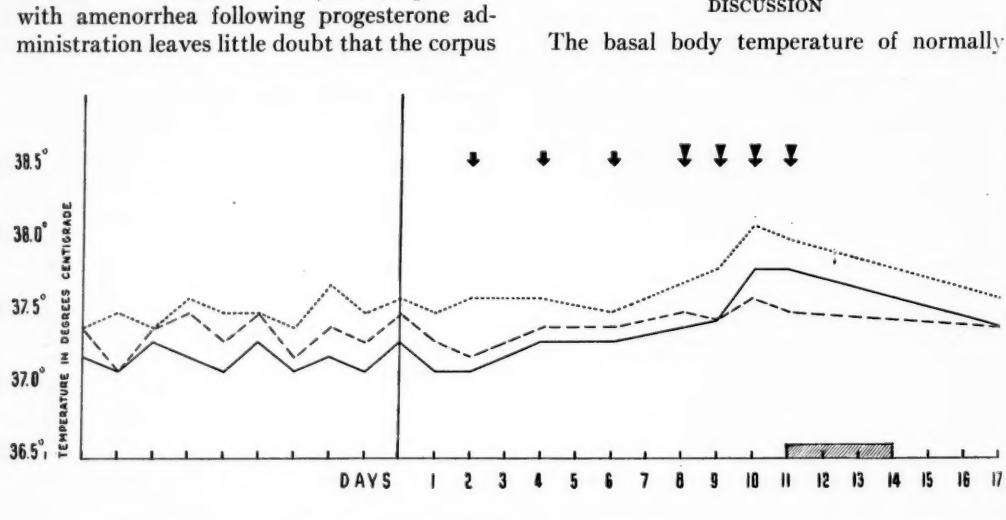

FIG. 6. Curves of corporal, vaginal and rectal temperatures recorded in amenorrhea of 8 months' duration prior to (left side of dividing line) and during hormone medication (right side of dividing line).

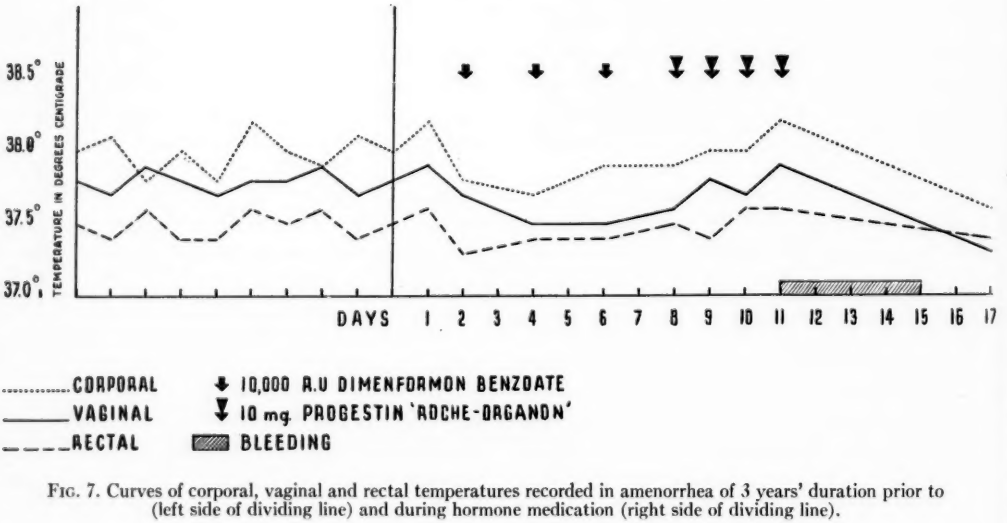

FIG. 7. Curves of corporal, vaginal and rectal temperatures recorded in amenorrhea of 3 years' duration prior to (left side of dividing line) and during hormone medication (right side of dividing line).

thus observed in the uterine body and cervix, the vagina, axilla, rectum and mouth. Since these fluctuations are of a cyclical nature, they may all be correlated to the ovarian cycle in the same way as changes occurring in the endometrial and vaginal epithelium.

There is a marked rise in temperature about the time of ovulation, the readings remaining generally on a higher level in the second half of the cycle with the premenstruum characterized by another peak. Following cessation of menstruation, the temperature drops to its lowest point. The mid-interval peak of the temperature may be regarded as a concomitant of ovulation. At this time there is a marked increase in the vascular filling of the uterine vessels which constitutes one of the etiologic factors for the rise in temperature. Among other factors influencing the temperature fluctuations are metabolic changes occurring rhythmically within the endometrium. The blood supply of the uterus reaches another peak premenstrually and this again is reflected in a rise of the uterine temperature before onset of menstruation. The uterine blood supply is lowest after cessation of the flow and consequently there is a postmenstrual drop in the uterine temperature.

Hyperemia and rise in temperature are more marked in the corpus itself, the focus of hormonal influence, than in the cervix or the vagina, and of course more so than in body cavities such as the rectum and the mouth. Therefore, corporal measurements are undoubtedly more reliable for studying and appraising the cyclical wave-like temperature fluctuations than measurements taken vaginally, rectally, or by mouth, notwithstanding the parallelism between the vaginal, rectal, and oral temperatures on the one hand and those of the uterus on the other. For practical purposes, however, the basal body temperature will also reflect the ovarian activity.

The fluctuations in the uterine temperature of climacteric women and of patients with amenorrhea are by no means so pronounced or so typical as they are in normally menstruating women. There is conspicuous absence of any marked peaks. Generally higher temperature levels are observed in women who have gone through their menopause many years before and in those with amenorrhea of long standing. These higher levels as compared with temperature levels in women whose amenorrhea—be it physiological or pathological—is of short duration may be explained as follows.

Aside from hormonal influences, the state of blood supply and metabolic changes, the heat exchange plays an important role in affecting the uterine temperature. In a-functional cases of long standing, due to involutional changes of the cervix, there is comparatively little loss of heat. Also, in these cases the thermometer comes to lie closer to the vascular layer of the corpus than it does in women in whom the involutional process has not progressed to such an extent.

SUMMARY

A thermometer is described which permits taking of uterine temperatures. The uterus as the immediate receptor organ of hormonal ovarian impulses more distinctly reflects temperature changes than does the rectum. Therefore utero-thermometry permits our studying the temperature fluctuations in the female in a more reliable way than rectal measurements. The new technique was employed in 32 normally menstruating women, in 24 women in the menopause, and in 36 patients with secondary amenorrhea. The findings are analyzed and discussed. Certain deviations from the normal pattern of the temperature curve encountered in ovarian deficiency cases are normalized by hormone administration.

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Evaluation of Sex Hormones in the Treatment of Benign Prostatic Hypertrophy, Carcinoma of the Prostate and Other Diseases of the Genito-Urinary System[1]

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MANY STARTLING observations have been reported from the use of the sex hormones in the treatment of genito-urinary diseases. In some instances, the reports have been so conflicting that a general feeling of confusion has developed among many physicians concerning the proper indications for the clinical application of these hormones.

CARCINOMA OF THE PROSTATE GLAND

Recent statistics show that up to 15 per cent of men beyond the age of 55 years develop carcinoma of the prostate. Many different forms of treatment have been advocated and intensive efforts made to treat this disease successfully. In advanced prostatic cancer, little encouragement has been found from any method of therapy. It is generally agreed by urological surgeons that in early carcinoma of the prostate, that is, where the disease is confined within the limits of the gland itself, radical perineal prostatectomy is the proper procedure. Unfortunately, this group of patients is very much in the minority as compared to the group in whom the disease has extended beyond the borders of the gland by the time the patient presents himself to the physician for the relief of his trouble.

The recent endocrine theories of Huggins *et al.* (1–3) in the treatment of advanced prostatic cancer have been widely accepted. In general, their investigations reveal that cancer of the prostate is often extremely sensitive to the male sex hormone. The presence of this material in the body activates the growth of prostatic cancer; in many patients, the inactivation of the male sex hormone brings about a retrogression of the cancer cells. This can be accomplished in two ways: (1) by castration; (2) by the administration of estrogens. There is at the present time some difference of opinion as to whether these two forms of therapy accomplish the same clinical result. For instance, it is well established in experimental animals that castration increases the gonadotropic activity of the anterior lobe of the pituitary. The production of androgens is under the influence of this principle. It is also thought that other organs beside the testis, notably the adrenals, are capable of producing androgens. It can be seen, therefore, that castration would not inactivate all the androgens, but might even increase the production of androgens in other organs. On the other hand, the administration of estrogens is believed to inactivate the production of androgens by depressing the gonadotropic activity of the pituitary. This form of therapy, then, would be more likely to inactivate the production of androgens in all parts of the body. It will be extremely interesting to compare the ultimate results of these two forms of therapy in prostatic cancer.

Submitted by request.

[1] Presented before the Session on Endocrinology, American College of Physicians, Chicago, Illinois, on October 12, 1943.

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Clinical Response of Advanced Prostatic Cancer to Estrogenic Therapy

In this series of patients, no effort has been made to compare the efficiency of estrogenic therapy with that of castration. Since April, 1941, 24 patients with advanced prostatic carcinoma have been treated with diethylstilbestrol.[3] The usual dose of this material was 1 mg. three times a day by mouth, although in some instances much larger doses—up to 15 mg. a day—were given. The diagnosis of advanced prostatic cancer was made from the rectal findings, x-ray evidence of metastasis, and, in a majority, histological sections of the prostatic tissue were obtained before estrogenic therapy was started. There were several patients in whom the histological reports of the prostate made elsewhere were used.

upon 19 patients and a suprapubic cystotomy was done in one patient before estrogenic therapy was started. Following the administration of diethylstilbestrol, the most striking and spectacular improvements in about 50 per cent of the patients were the disappearance of pain, gain in weight, and increase in appetite. This is best illustrated by the two bed-ridden patients, W. H. and F. K. Their pain had become so severe that morphine was required. W. H., who has had diethylstilbestrol since April, 1941, is now working eight hours a day, is completely free of pain, and has gained 37 lbs. in weight. F. K., who has had the same treatment since January, 1943, is likewise free of pain, working at odd jobs, and has gained 28 lbs. in weight.

However, not all of the patients showed such

TABLE 1. 24 PATIENTS WITH ADVANCED PROSTATIC CANCER TREATED WITH DIETHYLSTILBESTROL
(Ages 56 to 81 years)

Length of time observed		Amount of hormone		Metastases		Results		
6 months	9 pts.	500 mg.	11 pts.	Bones	16 pts.	Improved	14 pts.	(58.3%)[1]
7–12 months	5 pts.	500–1000 mg.	7 pts.	Lymph glands	4 pts.	No change	4 pts.	(16.6%)
13–24 months	6 pts.	1000–2000 mg.	4 pts.			Dead	6 pts.	(25.0%)
25–34 months	4 pts.	2000–3000 mg.	2 pts.					

[1] The term "improved" denotes the disappearance of pain; gain in weight; increased appetite. The prostate and periprostatic extension of the cancer became softer and in many instances smaller.

In general, the patients presented a pathetic and sorrowful picture. Pain was the prominent symptom. Loss of weight and appetite, difficulty in voiding, frequency, urgency, pyuria, dysuria, and hematuria were common complaints. Two were bed-ridden. Seven of the 24 patients in the series had previously had a prostatic operation; two patients had had a radical perineal prostatectomy; five patients had had one or more transurethral resections.

Results of Therapy. It should be recognized that it will do little good to castrate, or to prescribe estrogens to a patient with advanced prostatic cancer and then let him die from renal insufficiency caused by chronic retention of urine from prostatic obstruction. The obstruction should be removed, and this can best be done by a transurethral resection. In the present series, this operation was performed

[3] The diethyl stilbestrol was generously supplied by The Upjohn Company.

remarkable improvement. Six patients (25%) died, during treatment, from the disease. Four patients (16.6%) are not improved. There are 14 patients (58%) who have been definitely benefited by this form of therapy. They have been relieved of their pain, gained weight, and have all the appearance of well-being. In ten of the patients who are improved, the prostate and periprostatic tissue, which was hard and nodular from the extension of the carcinoma, is much softer and in many instances smaller. However, in all the patients the prostate examined per rectum has not returned to normal. Likewise, in the two patients who have been under observation the longest, there is still evidence of bone metastasis. Table 1 summarizes the clinical course of the 24 patients.

Untoward Effects during Treatment. These were mild and of no importance in comparison to the clinical improvement that occurred. We have previously shown that in the human (4–6)

impotence, sterility, gynecomastia, and complete disappearance of semen takes place during the administration of diethylstilbestrol; also increased pigmentation, especially of the nipples and on the ventral surface of the penis, develops. Occasionally, leg cramps may occur. There was no evidence of jaundice or severe gastro-intestinal symptoms in this series.

Present Status of Therapy

When should estrogen therapy be started? How much should be given and how long should it be continued? These questions cannot be definitely answered at the present time. It is possible that treatment should begin as soon as the diagnosis of prostatic cancer is adequately established. Whether the patient with early prostatic cancer in whom a radical perineal prostatectomy has been performed should also be treated with estrogens is still an open question. Obviously, if the cancer has been completely removed and no metastasis has occurred, the administration of estrogens would serve no purpose. However, there is no method at the present time, including the phosphatase test, that can determine the presence or absence of early metastasis.

The optimum dose of estrogenic hormone that should be given is not definitely known. At least 3 mg. of diethylstilbestrol a day has been advocated by some. It would appear that the amount to be used might depend on the extent of the carcinoma. We have been of the opinion that much larger doses are more efficacious in the patients in whom the metastasis is extensive.

It is also not known how long treatment should be continued—possibly indefinitely provided no serious reactions arise; even then, it could be instituted again as soon as the welfare of the patient permitted. However, the answer to these questions is still debatable. It will perhaps be some little time before a definite statement concerning the amount of hormone, length of treatment, and proper time to begin treatment with this form of therapy can be made. Although the time is still too short to evaluate end results, it can be said that patients with advanced prostatic cancer may be made more comfortable and perhaps live longer with this form of therapy than others previously used in this condition.

BENIGN PROSTATIC HYPERTROPHY

This is a common disease in elderly men. About 35 to 40 per cent of men reaching the age of 60 years will develop some signs and symptoms of prostatic obstruction. Practically all the hormones and especially the sex hormones have been advocated for treatment. Many favorable results have been reported from the use of the male sex hormone. However, in our experience, this material is of no value in the treatment of benign prostatic hypertrophy. In a previous publication (7), we have shown that testosterone propionate in total doses up to 3990 mg. given over a period as long as 56 weeks, produced no clinical improvement in a series of 23 patients.

Likewise, the histological character of the prostate in the treated patients was no different from that observed in untreated ones. Continued observations with this material in the treatment of prostatic hypertrophy have substantiated these findings.

More recently, enthusiastic results from the use of estrogens, especially diethylstilbestrol, have been reported. It has been adequately demonstrated that this material has a striking effect upon the glandular structure of the human prostate. However, in a series of 33 patients with benign prostatic hypertrophy treated at the Central Free Dispensary with estrogenic hormones[4] we have not been impressed with the clinical improvement from this form of therapy.

Clinical Response to Estrogenic Therapy

Thirty-three patients were observed for a sufficient length of time to make the following observations. The criteria used to establish the diagnosis of prostatic enlargement are those well known to all urologists., i.e., history, rectal examination, cystoscopy, and estimation of residual urine. The diethylstilbestrol was given by mouth, usually 1 mg. three times a day,

[4] Thirty-one patients had diethylstilbestrol; 1 patient had ethinyl-estradiol, 73 mg.; 1 patient had alpha-estradiol, 200 mg. The material for the last two was generously supplied by the Schering Corporation.

although up to 10 mg. a day was given to a few. The patients fell into two groups. *Group 1* was comprised of 27 patients who had the signs and symptoms of early prostatic obstruction. The prostate gland was enlarged from 1 plus to 2 plus, and the residual urine varied up to 60 cc. The cystoscopic examination revealed definite obstruction around the neck of the bladder in the form of lateral lobe hypertrophy, middle lobe enlargement, or both. No patient was included, no matter how severe his urinary symptoms, unless the cystoscopic examination showed definite evidence of prostatic enlargement. The average age of the patients in *Group 1* was 63.49 years; the youngest 50 years and the oldest 75 years. They were treated from 28 days to 498 days, receiving the hormone in amounts ranging from a minimum of 84 mg. to a maximum of 1320 mg.

The results of the therapy can be discussed under two headings—the decrease in size of the prostate and the improvement in the urinary symptoms. In seven patients, it was believed that the prostate had decreased slightly in size. There were five patients in whom the urinary symptoms of day frequency, nocturia, hesitation, dribbling, and difficulty in starting the stream were lessened. However, two patients in whom the urinary symptoms improved showed no change in the size of the prostate per rectum. We could not demonstrate by cystoscopic examination any decrease in the size of the prostate in any of the patients following treatment.

Group 2 consisted of six patients, the youngest 63 years of age, the oldest 75 years of age, and the average age was 71.16 years. Their residual urines varied from 60 cc. to 1000 cc. The prostate gland was enlarged from 2 plus to 4 plus. They received treatment from 49 days to 456 days, receiving from 200 mg. to 1774 mg. Five in the group have been hospitalized and the obstruction relieved by transurethral resection in four and a suprapubic prostatectomy in one. One patient is still under observation, and although his prostate has decreased in size per rectum he still has difficulty in voiding. Of the five patients who were hospitalized, the prostate gland was thought to have decreased in size in three patients. However, all of the patients did not completely empty their bladders and the symptoms of urinary obstruction still persisted. No change in the size of the obstruction following treatment could be observed by cystoscopic examination.

The following abstract of a case in *Group 2* can best summarize this form of therapy in patients with advanced prostatic obstruction.

C. G., a white man aged 75, presented himself at the Central Free Dispensary in April, 1942. He complained of marked frequency of voiding, urgency, pyuria, and a small stream, the symptoms having been present for two years. In the preceding month, he had developed an acute retention of urine and since then had catheterized himself twice a day. There were no other details of consequence in the past history.

The important physical findings revealed the patient to be thin, poorly nourished and anemic. The prostate was greatly enlarged, 4 plus, smooth and firm. There was 1000 cc. of residual urine. It was thick with pus cells and foul-smelling because of the presence of colon bacilli. His blood pressure was within normal limits. The total non-protein nitrogen was 43 mg. per 100 cc. of blood. A Wassermann reaction was negative.

Clinical Course. He was placed on 1 mg. of diethylstilbestrol three times a day, on April 28, 1942.

There was no change in his condition until June, 1942, at which time he did not need to use the catheter. His appetite improved and there was no nausea. By July, 1942, the stream had become stronger; the urine still had a strong odor and was filled with pus cells. He had 180 cc. of residual urine. There were no erections; the breasts were sore; the rectal examination revealed the prostate to be definitely smaller—about 2 plus. He complained of a little dizziness, and of cramps in the legs and feet.

By August, 1942, he voided four to five times during the day and the stream was good. The breasts were still tender; there were no hot or cold flashes. The residual urine varied from 240 cc. to 280 cc. and was still infected. The prostate was about the same size as in July. There were still cramps in the legs and toes.

By November, 1942, the patient had taken 588 mg. of diethylstilbestrol. He complained of attacks of dizziness and weakness and nausea. The medicine was discontinued.

In December, 1942, the residual urine was 210 cc. and contained many pus cells. There were no leg cramps. The breasts were no longer tense or full. The appetite was good. In February, 1943, the prostate had again become enlarged 3 plus. His stream began to be weak and there was difficulty in voiding. The residual urine was 240 cc. He was again given diethylstilbestrol, 0.5 mg., three times a day.

In May, 1943, the enlargement of the prostate had decreased to 2 plus, and the residual urine was 110 cc. The daily dose of diethylstilbestrol was increased to

1 mg. three times a day until June 29th, when it was again discontinued because of weakness and exhaustion upon slight exertion.

During July and August, 1943, the residual urine never was below 100 cc. On August 31, he was again started on 1 mg. of diethylstilbestrol twice a day. The residual urine varied from 150 cc. to 220 cc.

He entered the Presbyterian Hospital on October 5, 1943, for a transurethral resection. He had been under observation for 524 days and had received 1089 mg. diethylstilbestrol in 383 days. At this time, his blood pressure was 117/78; the hemoglobin was 13.5 grams;

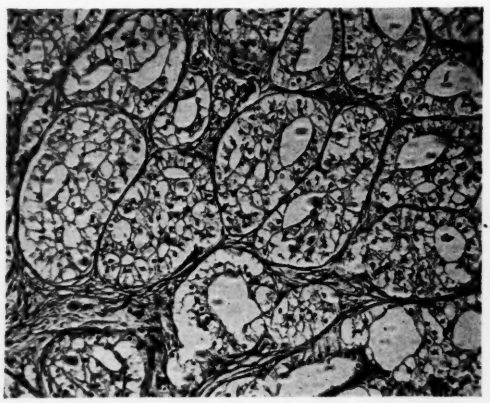

FIG. 1. Photomicrograph of a section of prostate gland from C. G. after the administration of 1089 mg. of diethylstilbestrol over a period of 524 days. Note that the cells of the glandular structure are vacuolated and in many places almost empty.

the red blood count, 4,280,000; the white count, 14,150. His total non-protein nitrogen was 32 mg. per 100 cc. of blood. The urinalysis showed the specific gravity to be 1.010; pus cells, 4 plus; albumin, 0; sugar, 0. The residual urine was 220 cc. The rectal examination showed the prostate to be enlarged 4 plus.

A plain x-ray plate of the genito-urinary tract revealed no evidence of stones. The cystoscopic examination revealed generalized, coarse trabeculations of the entire bladder, with many superficial cellules. There were two huge lateral lobes. An in-dwelling urethral catheter was placed in the bladder.

A transurethral resection was done four days after he entered the hospital and he was discharged five days after the operation, voiding freely and emptying the bladder completely.

The microscopic studies of the prostatic tissue, stained with hematoxylin and eosin, reveal the epithelium of the hyperplastic acini to be very pale. The cells appear large, vacuolated and almost empty (fig. 1). There is no unusual change in the fibro-muscular tissue. Figure 2 also shows a section of the prostate gland from one of the patients in *Group 2*. Here again can be seen the extensive alteration in the acini.

Present Status of Therapy

Although the estrogens produce improvement in the urinary symptoms in some of the patients, it must be remembered that many patients with prostatic obstruction will show similar improvement from the use of sitz baths and alkalies. On the other hand, the administration of estrogens in contrast to androgens produces extensive degenerative changes in the glandular structure of the prostate, which no doubt is responsible for the decrease observed

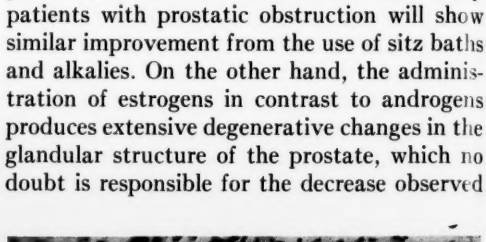

FIG. 2. Photomicrograph of a section of the prostate gland from C. S. (age 69, *Group 2*) after treatment. No improvement in urinary symptoms after the administration of 801 mg. of diethylstilbestrol in 268 days. Note marked hydropic degeneration of glandular structure.

in the size of the gland in some patients. However, these alterations are only temporary. When the estrogen is discontinued, the glandular structure again regenerates. Also, in the patients with a high residual urine, this form of therapy has given them only partial relief at best. It would seem, therefore, that estrogenic therapy is not the treatment of choice for such patients and operative procedures are still necessary.

IMPOTENCE

This is one of the common sex disorders. Although prevalent in elderly men, it also occurs frequently in young men. Impotence

should not be confused with sterility. A man may be partially impotent but not sterile, and, conversely, he may be sterile and not impotent. It must be constantly realized that impotence may be the symptom of a disease and not a disease in itself.

Just as there are many causes of impotence, so many and varied are the types of treatment that have been recommended for its cure. Careful examination of impotent patients will fail in most instances to reveal any organic disease. Psychic disturbances are a common cause.

The use of hormones, and especially testosterone propionate, has been strongly recommended for the treatment of this condition. It has been quite clearly shown that the administration of this material is efficacious in the treatment of impotence caused by a deficiency of natural testicular hormone, which is best illustrated in patients with hypogonadism, associated with eunuchoidism, Fröhlich's syndrome, or other developmental defects of the testes. However, in impotent males without any evidence of hypogonadism, it is difficult to see how the use of the male sex hormone could improve this condition. In order to evaluate the effect of this material upon such patients, a group of elderly men at the Central Free Dispensary was observed. It was felt that men over 40 years of age would be a more desirable group in whom to observe this form of therapy because they would be more likely to have a deficiency of male sex hormone than would a younger group. Adequate urological and general examinations and laboratory procedures were carried out to eliminate any organic disease that could be the cause of the impotence. If any were found, such patients were not included.

The testosterone propionate[5] was given intramuscularly, 10 to 25 mg., three to four times a week. Thirty-one patients with complaints of either partial or complete impotence were observed from 4 to 84 weeks. The average age was 51 years. The minimum amount of this material received by a patient was 185 mg. and the maximum amount, 5105 mg.

From this therapy, there was little if any improvement, except in two patients. One was a heavy, obese, fifty-five-year-old man who was completely impotent. His genitalia and testes were normal. This patient showed a spectacular improvement after he had received 100 mg. of the testosterone propionate, which continued while he was under treatment for a period of 21 months. He received a total of 2530 mg. The improvement apparently was not psychic for the reason that when he was placed on placebos, his impotence recurred. The other noteworthy response was in a patient 51 years of age who received 350 mg. in 12 weeks. He was partially impotent. The remaining 29 patients received no benefit from this therapy.

[5] The testosterone propionate was generously supplied by the Schering Corporation.

PREMATURE EJACULATIONS

These may or may not be associated with poor erections. It is one of the most common sex complaints in young men. If severe, it can be responsible for a sterile marriage. The causes are many. Local inflammatory lesions such as prostatitis with a posterior urethritis may be responsible. If there is no evidence of a local inflammatory lesion or the condition is not associated with poor erections, the administration of small doses of diethylstilbestrol—0.5 mg. per day for six or eight weeks—has proved efficacious in some instances.

MALE CLIMACTERIC

This condition, it is said, usually occurs in men over 50 years of age and is characterized by gradual decline of sexual power, nervousness, insomnia, exhaustion, hot and cold flashes, and a mild type of psychosis. It must be borne in mind that there is not a definite loss of sex function in the male that corresponds to the menopause in the female. For instance, spermatogenic activity occurs regularly in men over 70 years of age. While it is difficult to prove that such a syndrome as male climacteric does not exist, it should be emphasized that a critical evaluation of a patient's symptoms should be made before he is given a series of hormonal treatments. In general, the same line of thought holds concerning rejuvenation. The waning of sexual drive and power is a natural physiological process that occurs with advancing age. It is very questionable whether any hormone is

of value in individuals who are attempting to overcome this normal process.

SUMMARY

The use of sex hormones for treatment of genito-urinary diseases is discussed. Clinical data are presented to substantiate the following conclusions.

About 50 per cent of patients with advanced prostatic cancer are greatly improved by estrogenic therapy. The time elapsed since treatment is yet too short to evaluate end results.

The treatment of prostatic hypertrophy (associated with bladder insufficiency) is still a surgical procedure, even though the administration of estrogens to such patients produces extensive temporary alterations in the glandular structure of the prostate.

There should be a thorough search for the causes of impotence and other sex disorders before a course of hormonal therapy is given.

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Problems Involved in the Diagnosis and Management of Male Infertility[1]

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IN RECENT years, it has become apparent that male sterility is much more common than was once supposed. Up to a few years ago, the wife shouldered the blame for the childless marriage. However, we now know that the causes for such a condition are about evenly distributed between the wife and the husband. The problem involved in attempting to discover the cause of a barren marriage may be exceedingly difficult. The problem is complex because of the multiplicity of factors that may be present in the male and female and the difficulty of evaluating just where the responsibility for the sterile marriage may lie. In the study of a sterile couple, it is not only necessary to demonstrate the sterility itself, but also to arrive at an estimate of the relative fertility of each partner and raise the existing fertility, if possible, to a level at which conception may occur.

The examination and the investigation of the husband can be divided into two parts: the clinical study and the analysis of the seminal fluid.

CLINICAL STUDY

The clinical study should include a well-organized, careful history and physical examination, which can be divided into the following parts.

Genital History. The important points are: previous attacks of gonorrhea and epididymitis, orchitis, mumps, injuries to the testes, infections of the prostate, tuberculosis of the genital system, strictures of the urethra, congenital abnormalities—such as undescended testis—hypospadias, and epispadias.

Sexual History. The main purpose is to determine the ability of the patient to deposit the semen in the vaginal vault and the frequency with which he can do so. Such things as poor erections and premature or painful ejaculations are common sexual complaints and may be either organic or psychic in origin. Hematospermia usually indicates an infection of the prostate. A rare symptom is aspermia. Peyronie's disease, in which the penis bends or curves upwards during an erection, may be the condition from which the patient seeks relief.

General and Endocrine History. A survey should be made of the patient's life up to the time of study. Previous illnesses, such as infectious diseases, x-ray treatments—especially over the genital regions—and previous operations should be checked.

Notations are made concerning dietary deficiencies, foci of infection, gain or loss in weight and the habits of living. Although a sedentary or highly geared life may temporarily influence the quality and quantity of spermatozoa, far too frequently the patient with infertility is advised to take a prolonged holiday, which is by no means a cure for his condition. Special attention should be paid to any signs or symptoms of an endocrine dysfunction, such as Fröhlich's syndrome, eunuchoidism, thyroid disturbances, diabetes, and especially pituitary disorders. Minor dysfunctions of the pituitary gland cannot be recognized and must be determined by a system of trial and error; but many times gross findings are uncovered that point to this gland as the seat of the disturbances.

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Physical Examination. This should include a thorough search for the causes that have been enumerated in the history. It should begin with the head and end with the feet. Measurements should be made whenever possible. The distribution and the amount of hair, body contour, and stature should be observed closely.

Genital Examination. The size, shape, and consistency of the testes should be carefully noted. Frequently atrophic testes will be found, which condition will give a clue to the cause of the sterility. The presence of a varicocele or an old operative scar—especially the scar of a herniotomy, in which the vas deferens may have been damaged—must be taken into consideration. Nodules and masses are searched for in the examination of the epididymides and the vas deferens. The shaft of the penis is examined for the presence of hard, fibrous plaques indicative of Peyronie's disease; this can prevent the semen from being deposited in the vaginal vault. Exploration of the urethra with sounds is made for the presence of strictures, which, if present, may prevent the emission of the semen.

Examination of Accessory Glands. The prostate and the seminal vesicles are to be examined by rectal palpation; massage of the prostate and an examination of the prostatic fluid are necessary. Normal prostatic fluid contains only a few leucocytes per high-power field. The presence of 20 or more denotes infection, which should be cleared up by bi-weekly massage. Spermatozoa or their absence in the prostatic fluid have no clinical significance.

Laboratory Tests. The usual laboratory studies, such as a blood count, hemoglobin, differential count, blood pressure, urinalysis, Wassermann or Kahn test, and basal metabolism are routine procedures. Special laboratory tests should be made if indicated; a few examples are roentgenological studies of the sella turcica and the extremities, pyelography, urethroscopic and cystoscopic examinations, and testicular biopsies.

Testicular Biopsy. This procedure is necessary only when more information is desired concerning the state of the seminiferous tubules than can be obtained from the analysis of the semen. For instance, in a patient with azoöspermia it may be of value to know whether the cause is primarily in the spermatogenic cells or an obstruction or atresia in the conveying system. A biopsy is not difficult to carry out and if ordinary surgical precautions are taken, no complications occur. The procedures should be thoroughly explained to the patient.

The technique is as follows. Under local anesthesia, a small incision about 1 cm. long is made over the aspect of the scrotum. An assistant should hold the testis so that its outer border is pressed firmly against the skin. After the outer layer of the tunica vaginalis is open, the white, glistening covering of the testis comes readily into the incision. A small, wedge-shaped piece of tisssue can be removed without difficulty or injury to the testis. The edges are sutured with fine No. 1 catgut and the skin closed with two stitches of silk. The piece of tissue should be placed immediately in Bouin's solution. Histological sections are stained by any of the well-known methods but Heidenhain's iron-hematoxylin stain is an excellent one to use for cell mitosis.

SEMINAL FLUID ANALYSIS

The final diagnosis of the relative sterility or fertility of a man can be made only by an appraisal of the seminal fluid. This is as important in evaluating spermatogenic activity as are blood studies in the diagnosis of a blood dyscrasia. It is the collocation of all the information gained from the semen analysis that is important; the parts of the analysis are in themselves of little individual value. In a microscopic field, fresh spermatozoa can be likened to the population of a small city—there is a great variation in the rapidity of movement and also the type and character of movement; in other words, they do not all perform alike.

In order to be practicable, the technique should be simple enough to be used in an office laboratory.

Method of Collecting Specimen. Of the various methods advocated for obtaining the seminal fluid, the best procedure is to have the patient ejaculate directly into a dry, glass container after four or five days of sexual inactivity. Most of the volume of the seminal fluid is made up of secretions from the prostate and seminal vesicles and the amount is variable. Usually 2–4 cc. is considered normal although higher

volumes are frequently obtained. When examined immediately after ejaculation, the normal semen is a coagulated jelly. It usually liquefies in 10 to 20 minutes and has a translucent appearance. The pH can be tested accurately enough for clinical work by using any one of the color methods; in normal specimens it is from 7.5 to 8.0. A low pH, which is extremely rare in my experience, may influence the viability of spermatozoa. The semen is best preserved in a refrigerator. The addition of a small crystal of thymol will keep it in a suitable condition for a week or so.

Estimation and Viability of Spermatozoa. After the seminal fluid has liquefied, it is measured in cubic centimeters; a small drop is then placed on a glass slide and sealed with a cover slip and placed under the microscope. The motility and percentage of active spermatozoa are estimated by using the high-dry lens. Pus cells are searched for. Most semen specimens have an initial sperm motility of 50 to 90 per cent. The longevity of the spermatozoa can be determined by drawing a small amount into a fine glass tube, sealing both ends, placing it in an icebox, and making interval observations. Under ordinary icebox temperature, spermatozoa will be active up to 24 to 96 hours. Motility and longevity examinations are in themselves of very little value because abnormal sperm cells may be as motile as the normal. Necrospermia, in my experience, is exceedingly rare; I cannot recall a specimen in over 1500 examinations in which all the spermatozoa were dead. Usually, I think, such a condition is due to the technique employed in obtaining the specimen, or else too long a time has elapsed before it is examined.

Spermatozoa Count. A white-blood-counting pipette is used. A solution containing one per cent formalin and five per cent sodium carbonate in distilled water makes a good diluent. All of the spermatozoa in the four large squares of the counting chamber are enumerated, using the high, dry objective. The same calculations are used as for white-blood counts. The number is then multiplied by 1000 for cubic centimeters. The result obtained is the number of spermatozoa in 1 cc.; this, when multiplied by the amount of semen, gives the total number. Semen considered normal usually has at least 100,000,000 spermatozoa, although I have known pregnancies to occur in several wives when the sperm counts of the husbands were below 25,000,000.

Differential Spermatozoa Count. Many different stains can be used; the following is from Cary and Hotchkiss. A film of seminal fluid is spread upon a slide, applying the method for making blood smears. When dry, the film is fixed by immersing the slide in Schaudinn's solution. The procedure is as follows.

Immerse the slide for one minute in a solution containing two parts of a 7 per cent mercuric chloride solution to one part of absolute alcohol and then for one minute in 50 per cent alcohol; next, immerse for $2\frac{1}{2}$ minutes in a solution composed of 2 drops of tincture of iodine in 3 ounces of distilled water. Wash in tap water. After the preparation has been fixed, it is stained with eosin and hematoxylin, using the following procedure.

Immerse the slide for $\frac{1}{2}$ minute in a 5 per cent aqueous solution of eosin and then for $\frac{1}{2}$ minute in a solution containing 2 drops of hydrochloric acid in 3 ounces of water. Wash in distilled water. Immerse slide $2\frac{1}{2}$ minutes in hematoxylin and then for 1 minute in a solution of 2 drops of glacial acetic acid in 3 ounces of distilled water. Wash in distilled water and dry. By this method, the nuclei are stained blue and the cytoplasm is stained red. The stained preparation is then examined under the microscope, using the oil-immersion objective. At least 100 spermatozoa are examined and classified. Normal spermatozoa have a full oval contour or are only slightly tapered at the base; the tail may be coiled about the head or extended. It is thought by some that variations in the size of the normally constructed cells are not as important as nuclear abnormalities. Abnormal findings include microspermia, megalospermia, and spermatozoa that have no definite shape at all. Occasionally, spermatozoa are seen that have double bodies or tails. Finer distinctions of classification of abnormal spermatozoa are recognized.

There are many more extensive examinations, such as biometric, chemical, and metabolic studies of the spermatozoa. These are important and necessary for a more critical appraisal of the semen, but at the present time

are somewhat too elaborate for the ordinary office laboratory. If patients are under treatment, the semen should be examined about every six to eight weeks.

Post-coital Examination. This should be carried out as an adjunct to the examination of the semen. In this test, the spermatozoa are recovered after intercourse from the vagina and cervix and the percentage of live ones estimated. The purpose is to determine the influence of the vaginal and cervical secretions upon the viability of the spermatozoa.

By assimilating the results of these various procedures, a fairly accurate estimation can be made of the quality and quantity of the spermatozoa and an index obtained of the patient's fertility.

CLINICAL ANALYSIS OF PATIENTS

In a study of 100 married men between the ages of 20 and 55 years, most of whom were referred by obstetricians because of a barren marriage, the cause of the sterility was found to be present in 45 of them.

In another series of 65 men, between the ages of 23 and 42 years who had either an azoöspermia or an oligospermia—that is, a total sperm count of less than 60,000,000—we were able to discover the cause of the sperm deficiency in 30. Of these, 11 patients showed a marked endocrine disturbance—Fröhlich's syndrome, eunuchoidism, or hyperpituitarism; 6 patients had extensive bilateral atrophy of the testes from earlier mumps; 5 patients had had bilateral epididymitis following a Neisserian infection and all were azoöspermatic; 4 patients had bilateral undescended testes; 2 patients had previously been operated upon, and one of the two had active spermatozoa; 2 patients had syphilis; 1 patient had been treated extensively with x-ray therapy over the genital region for a tumor of the hip—he was azoöspermatic; large bilateral hydroceles were present in another patient.

In the second group, which consisted of 35 patients, no adequate causes could be found to explain their sperm deficiency. One patient had one undescended testis and the other testis was normal; three patients had relatively small testes; one patient had one atrophied testis, the other being normal. The remaining patients had normal genitalia. They were well-nourished, well-proportioned, healthy men, representing the middle class of our society. They indulged in moderate exercise. Dietary deficiencies or sedentary life did not appear to enter into the causation. All the various laboratory tests failed to reveal any cause that might have a bearing on their sperm deficiency. In our experience, it is this group in whom it is difficult to evaluate what form of therapy is best.

EFFECT OF HORMONES UPON SPERMATOGENIC FUNCTION

The relationship of the various endocrine glands, especially the pituitary and the testis, is now fairly well understood. It is known that the seminiferous tubules and interstitial cells of the testis are dependent for normal activity upon the gonadotropic influence of the anterior lobe of the pituitary. It is thought that there are two gonadotropic effects of the pituitary—one that influences the interstitial cells and the other primarily the seminiferous tubules. The removal of the anterior lobe of the pituitary will produce an atrophy of the testis, which involves both the interstitial cells and seminiferous tubules. This can be repaired by injections of active gonadotropic extract.

Clinical data concerning the effect of sex hormones and gonadotropins upon human spermatogenesis are conflicting. The reasons are obvious: accurate observations are more difficult to make upon the human than upon experimental animals.

Although it has been thought that the male sex hormone increases human spermatogenesis, it is now well established that this material produces a depletion of spermatozoa, associated with extensive degeneration of the seminiferous tubules (1). It has, however, no effect upon the volume of the seminal fluid (2).

The female sex hormone likewise produces an azoöspermia, accompanied by degeneration of the seminiferous tubules, similar to that observed following the use of the male sex hormone. In addition, there is a complete drying up of the seminal fluid because of the extensive alterations that take place in the glandular structure of the prostate and possibly the seminal vesicles (3). These effects of the two sex hormones are only temporary and the function

of the testis returns following the withdrawal of the hormones.

It is quite obvious, then, that the administration of the sex hormones would be contraindicated in a patient with a sperm deficiency. The male sex hormone, however, is indicated in those cases in which the sterility is associated with a hypogenitalism and hypogonadism. However, in such cases, we have not observed an increase in spermatogenesis; such patients, in our experience, usually have azoöspermia. There still is a difference of opinion concerning the effect of the various gonadotropins upon the spermatogenic function of animals and, likewise, opinions differ concerning the effect of these hormones upon human spermatogenesis. All three—the chorionic, equine, and pituitary gonadotropins—have been reported to increase spermatogenesis in man. In theory, the gonadotropin containing the follicle-stimulating principle should be the preferable one to use. However, clinical results so far do not substantiate this. We have been impressed by the number of patients with a marked oligospermia in whom no response occurred following the administration of any one of the three gonadotropins.

On the other hand, it would seem that there might be a disturbance in the pituitary-gonadal relationship in many of the patients with an unexplained oligospermia. In such instances, one would be justified in using one of the three gonadotropins. However, at the present time, the whole problem appears to be a "trial and error" procedure. Likewise, there is no guide for the amount, frequency, and length of time that the hormones should be used. Until more information is obtained from clinical observations, definite statements cannot be made.

SUMMARY

The methods of studying sterility that have proved to be most satisfactory are reviewed. A summary of findings in 165 clinical cases is included. The study serves to emphasize four facts.

The causes of a barren marriage are about evenly distributed between husband and wife.

Thorough examination of the seminal fluid is necessary in order to evaluate an individual's index of fertility.

The administration of sex hormones produces a depletion of spermatozoa.

The value of gonadotropins in the treatment of sperm deficiency is still uncertain.

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COMMUNICATION

EFFECT OF STILBESTROL ON BENIGN HYPERTROPHY OF THE PROSTATE

IN RECENT YEARS several convincing demonstrations have been put forth proving that prostatic carcinoma is a hormone-sensitive tumor. Huggins,[1] Alyea,[2] Nesbit,[3] and others resorted to castration, while Herbst,[4] Kearns,[5] and others obtained equally remarkable effects with the use of estrogens. These effects led us to formulate a plan for the investigation of the effect of stilbestrol on patients with benign prostatic hypertrophy at the Milwaukee County Hospital. Thus far two patients have been treated.

The initial test on each patient was a preliminary biopsy of both the testicle and prostate. Then followed the administration of stilbestrol* until 48 mg. and 51 mg. respectively were given to the two patients. No untoward toxic effects except gynecomastia were noticed. This breast thickening Kearns[6] considers a good criterion indicating that sufficient estrogenic effect is being maintained.

The diagnosis of benign prostatic hypertrophy was based on the history, general physical and rectal examinations, tests for residual urine, biopsy of prostate and testicle, and cystoscopy. Urological examination was completed by urinary cultures, blood chemistry, alkaline and acid serum phosphatase and renal function tests.

The two patients in this series presented histories of prostatism, retention, urinary difficulties and residual urine. A third patient on whom preliminary biopsy was made and followed by stilbestrol therapy experienced such improvement with decrease of residual urine that he refused further treatment and would not tolerate a repetition of biopsy. His prostate did not show any perceptible decrease in size up to the time of rectal re-examination.

The two patients on whom tests were completed experienced less difficulty in starting the urinary stream, less burning and, in the case of the second patient, a decrease in residual from two ounces to one ounce. Neither patient showed decrease in size of the gland detectable by rectal examination.

The histological changes after receiving stilbestrol were as follows:

Prostate

1—Decrease in height of epithelium lining the acini.

2—Decrease in size of acini.

3—Some hydropic degeneration of the epithelial cells.

4—Edema of interstitial tissue.

Testicle

1—Loss or marked decrease of spermatogenesis; flattening of the cells of the tubules and thinning of the walls of the tubules.

2—Interstitial tissue became edematous.

3—Tubules were widely separated.

4—Interstitial cells lay in small nests in the stroma but did not disappear.

It is quite obvious from our observations thus far that definite atrophy of the gland is produced, as shown by the histological changes. However, clinically the effect on benign hypertrophy is less striking, but that should not divert us from a thorough investigation of the effect of the various estrogens on the benign prostatic hypertrophy, even though it involves more prolonged observations over a number of months or even years.

SUMMARY

In three cases of benign prostatic hypertrophy improvement in clinical symptoms was experienced following the use of stilbestrol. In two of the cases in which biopsies were obtained shrinkage of prostatic tissues as well as evidences of depression of spermatogenesis were seen.

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* Encoats, brand of diethylstilbestrol, The Wm. S. Merrell Company.

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